REMARKS

Claims 1-53 are pending in this application. Claims 29-53 are withdrawn. Claims 1-4, 9-13, 16-19, and 22-26 are amended. Support for the amendments to these claims can be found, for example, in old claims 1-4, 9-13, 16-19, 22-26, and in the specification (see pg. 7, lines 18-21; pg. 8, lines 14-17). Reconsideration is respectfully requested in view of the following remarks.

I. Claim Rejection Under 35 U.S.C. 112, First Paragraph:

The Examiner rejected claims 1-28 under 35 U.S.C. 112, first paragraph, as being allegedly non-enabling for the claimed invention. Applicant traverses-in-part and has amended-in-part the instant claims to address this rejection.

The Examiner provides an analysis of the Wands factors for the proposition that it provides factors for analysis in determining when a disclosure for a patent application requires undue experimentation. The Examiner thus concludes that the factors presented provide that "undue experimentation would have been required at the time of the effective filing date of the instant application for one of ordinary skill in the art to reproducibly practice the full scope of the present invention, as claimed." See Office Action, pg. 5.

Applicants wish to point out that the amount of experimentation is only one of a lengthy list of factors that the Federal Circuit has suggested in determining whether the scope of claims in a patent application or patent are enabled by the disclosure. The list of the factors to be considered are:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Furthermore, the court in Wands states:

> It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *In re Wands*, 858 F.2d 731 at 737,740 (Fed. Cir. 1988).

In regards to the amount of experimentation needed to support an undue experimentation argument, the test itself "is not merely quantitative, since a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention." *Id.* at 736-740. Applicants submit that the specification provides sufficient guidance to enable the amended claims without undue experimentation in the instant application.

In addition, Applicants respectfully disagree with the Examiner's contention regarding botulinum toxin prior art. The Examiner points to Boroff et al. (pg. 1-62, in "Microbial Toxins" S Kadis, T. Montie and S. Ajl, eds., Academic Press, 1971) for the assertion that the stability of the claimed type B toxin liquid formulation within the full concentration range as recited in the instant claims. The Examiner claims that this is important because the art allegedly reports lack of clarity and contradictions on the subject of stability of botulinum toxins as related to various factors. Applicants submit that the Boroff et al. article does not represent the state of the art at the time of filing of the instant application.

The Boroff article, published in 1971, is a review of the state of the art in the 50's and 60's. The article presents work done on primarily partially purified extracts of botulinum toxin preparations (see pgs. 9-15). In contrast, the present application provides detailed guidance with respect to the isolation and purification of botulinum toxin complexes. The present application comprehends the need for purification from cellular proteases and contaminants, in contrast to the work cited in the Boroff article, in order to maintain the stability of the liquid formulation at the temperatures cited. Therefore, the Boroff article is not relevant to the state of the prior art at the time of filing, and does not support the Examiner's contention that there are contradictions on the subject of stability of botulinum toxins as related to various factors.

In regards to the Examiner's reliance on Gartlan et al. (Otolar-Head & Neck Surg. 108:135-140 (1993)) regarding the stability of botulinum toxin at pH 6.2 phosphate buffer, Applicants respectfully point out that the reference does not apply to the instant claims. The Examiner states that Gartlan supports art describing botulinum toxin solution stability at room temperature in phosphate buffer of pH 6.2 for only a few days. Applicants respectfully disagree with the Examiner that Gartlan supports this interpretation. As support, Applicants point to the article referenced by Gartlan, specifically to the work of Schantz and Kautter ("Standardized assay for clostridium botulinum toxins," J. Assoc. Off. Anal. Chem. 61:96-9 (1978), attached herein, which describe experiments in *freeze-thawing* of botulinum toxin solutions. As stated in the Gartlan article at p. 139, 2nd full paragraph, "Schantz and Kautter found that botulinum toxin can be *frozen and thawed* without appreciable loss of toxicity when buffered in a sodium phosphate solution of pH 6.2" (emphasis added). That Gartlan was speaking to results from freeze-thaw experiments is supported in the Schantz and Kautter article on p. 98, 2nd col., 1st full paragraph. In describing the experiments on sodium phosphate buffer, Schantz states "In this buffer the solution can be *frozen and thawed* without appreciable loss of toxicity." The instant application does not involve freeze-thawing of botulinum toxin solutions, a procedure that is known to those of ordinary skill in the art to be harmful to protein complexes. Therefore, Gartlan is not applicable to the instant claims.

Similarly, the Examiner's reliance on Schantz & Johnson (In "Therapy with Botulinum Toxin" Jankovic et al. eds., Marcel Dekker, Inc., New York, 41-51 (1994)) is also not applicable to the instant claims. The Examiner points to Schantz & Johnson for the contention that "purified neurotoxins, i.e., neurotoxins separated from the protective nontoxic proteins, exhibited poor stability." See Office Action, pg. 5. The protective nontoxic proteins are carrier proteins, and co-purify with the toxin chains to form complexes of similar size (900 kD) to the Schantz and Johnson stable Botulinum toxin A crystalline form. Compare Schantz & Johnson, pg. 44, last full paragraph to pg. 9, lines 2-4 of the instant application. Therefore, the Examiner's contention that there is no support for the stability of botulinum toxins other than type B is incorrect. The Examiner cannot compare evidence from other experiments that are not reflective of the conditions put forth in the instant application.

Applicants believe that they have provided extensive teaching regarding the purification of toxin, and preparing it in a formulation that is stable for extended periods of time. Purification of types A and B are described in detail in section III of the specification beginning at about page 10, line 22. As noted at page 12, line 22, toxin types C_1, C_2, D, E, F or G may be prepared and purified according to methods known in the art. One skilled in the art would understand how to adapt the disclosed methods to provide stable formulations comprising types A and C-G from reading the specification and references available prior to the filing of this application.

Based on the amendment to the claims and the remarks above, Applicants respectfully request withdrawal of this rejection.

II. Claim Rejections Under 35 U.S.C. 102(b) to Schantz et al.:

The Examiner rejected claims 16, 17, 21 and 27 under 35 U.S.C. 102(b) as allegedly anticipated by Schantz et al. (J. AOAC 61:96-99 (1978). It is believed that this rejection is not applicable in view of the present amendments to the claims.

The Examiner states that Schantz teaches a solvent composition in buffer having a pH of 4.2. See Office Action, p. 10. Applicants respectfully submit that Schantz does not disclose, teach or suggest a composition as provided in the amended claims. A pH of 4.2, as was disclosed in Schantz, is not within 10% of the recited limitation of pH 5-6. Schantz, therefore, does not anticipate the presently claimed compositions.

In light of the arguments presented above and the amended claims, Applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSION

In light of the remarks and amendments set forth above, Applicant believes that the claims are in condition for allowance. Applicant respectfully solicits the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

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